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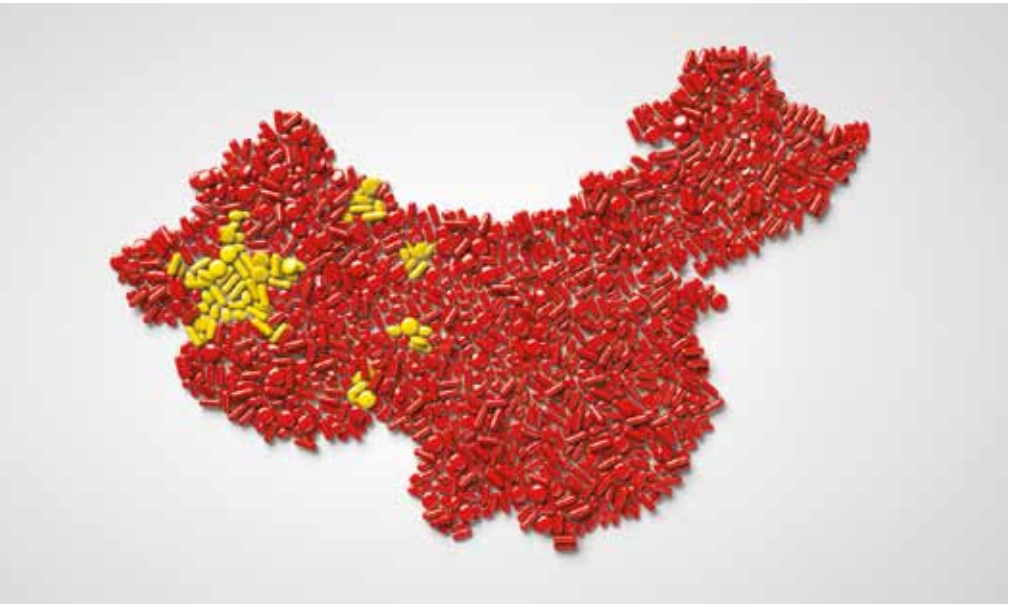

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Faster Reviews In China Benefit Multinationals And Patients

The China FDA's new priority reviews and faster approval procedures for innovative drugs are beginning to bear fruit, with multinationals and patients among the first beneficiaries from recent clearances from two novel cancer drugs in this large emerging market.

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Multinational pharma firms are among the first beneficiaries of China's newly introduced priority review pathway for new drugs, bringing more treatment options to non-small cell lung cancer (NSCLC) patients in the country through two recent approvals for irreversible epidermal growth factor receptor (EGFR) inhibitors.

Granted a marketing authorization approval at the end of March was AstraZeneca PLC's *Tagrisso* (osimertinib) 40 mg and 80 mg once-daily oral tablets for adult patients with locally-advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

Tagrisso is the first AstraZeneca medicine to be approved under the China FDA's priority review pathway, and was also remarkably a record-fast approval for an imported drug by the Chinese regulator. AstraZeneca spent less than two years to secure Tagrisso's local launch, as it filed a clinical trial application with the CFDA in June 2014 and received a priority review designation in September 2016. After an approval submission on Feb. 3 this year, Tagrisso was included on the priority review list on March 3.

The CFDA's Center for Drug Evaluation stated in a notice that "Tagrisso has significant therapeutic advantages compared with the existing treatments. After experts' review, the drug is entitled to enter the priority approval pathway directly."

George Chen, vice president and head of global medicine development at AstraZeneca China, said in a response on the company's product development strategy: "Aiming to achieve the rapid approval, AstraZeneca was proactively working with drug approval authorities and Chinese oncology experts at an early stage of development, to explore together the development strategies of Tagrisso in China".

GIOTRIF BLAZES TRAIL

Earlier in March, Boehringer Ingelheim GMBH also announced the approval in China of *Giotrif* (afatinib), an irreversible second-generation ErbB family blocker for patients with distinct types of NSCLC. Giotrif was the first imported drug to be approved under the priority review pathway and marked the German firm's entry into China's oncology market.

Giotrif received an Imported Drugs License for two indications: locally advanced or metastatic EGFR mutation-positive lung cancer patients who have not received any prior therapy with TKIs; and patients with locally advanced or metastatic squamous

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from the editor

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Unusually among global protest movements, March for Science (taking place on 22 April in 54 countries) could see large chunks of pharma's workforce at the placard-wielding forefront. But will the industry's top leaders speak out in favor of the rallies?

Some scientists fear that the movement, whose initial central impetus was to march specifically on Washington DC, risks politicizing science because of its anti-Trump overtones and ongoing squabbles over its diversity message. The worry is that by entering an already heavily polarized fray, the pro-science brigade will preach to the converted while alienating those it is in most need of winning over. The politicization risk is not just in the US: it could be seen as anti-Brexit in the UK, for example.

Still, as pharma well knows, mistrust of science is a serious problem (think of anti-vaxxers), and this global mobilization at least opens a new type of debate in which science itself – rather than some societal ill it is perceived to have spawned – is the topic. A discussion that pivots on science generally as a public good rather than specific instances of collateral damage: surely that's worth supporting.

exclusive online content

Biomunex CSO Defines Lead Compounds, Early R&D Plans
Eugene Zhukovsky, chief scientific officer at Biomunex, talks about the company's clinical development strategy of using monospecific antibodies as building blocks for next generation cancer therapies.
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Harnessing AI For Drug Development – UK's BenevolentAI And MRCT Link
The hope artificial intelligence can revolutionize current drug discovery methods will be tested in a new collaboration between UK-based BenevolentAI and the medical research charity MRC Technology.
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56 Biosimilars In Late-Stage Development Line Up To Challenge Top Biologic Drugs

Many key biologic drugs, including adalimumab, bevacizumab, rituximab and trastuzumab, are facing biosimilar competition from products that have been either filed or recently approved in Europe, and 56 biosimilars are now at a late stage of clinical development, according to Per Troein of QuintilesIMS.

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56 biosimilar products are in late-stage development at global level, 47 of which are in Phase III trials and nine at the pre-registration stage. The top diseases being targeted are autoimmune disease (27 of the late-stage 56 products) and oncology (24), followed by diabetes (four), respiratory disease (two) and others (three). 68 biosimilars are at the preclinical stage, 14 are in Phase I trials and three are in Phase II.

The figures were presented by Per Troein, vice-president strategic partners at QuintilesIMS, during the recent Medicines for Europe annual biosimilars conference in London. He said that "the leading biological products on a global basis will have competition from biosimilars very, very soon."

Key products facing biosimilar competition in Europe – those for which biosimilar versions have been filed with the European Medicines Agency or have recently been approved – include AbbVie Inc.'s *Humira* (adalimumab), with European sales of €3.4bn in 2016, Amgen Inc.'s *Enbrel* (etanercept, €2bn), Roche's *Herceptin* (trastuzumab, €1.8bn), *Avastin* (bevacizumab, €1.8bn) and *MabThera* (rituximab, €1.7bn), Sanofi Sanofi's *Lantus* (insulin glargine, €1.1bn), and Amgen's *Neulasta* (pegfilgrastim, €0.5bn), Troein said.

He also noted that the EU accounts for just a quarter of global biologic drug sales by value, but it represents the lion's share – 87% – of biosimilar product sales. By contrast, the US, the world's biggest market for biologics, accounts for 60% of biologic sales but for only 3% of the biosimilars market. Japan is much smaller on both counts: 6% of global biologic sales, and 8% of biosimilar sales.

MARKET GROWTH

Turning to the current market shares in Europe, Troein said that for EPO, for example, in many European countries biosimilars represent around 50% of the total market. "Look at G-CSF instead, and you see it has been much more dominant – for filgrastim in many countries the market "is largely totally supplied with biosimilar products."

As for the price effect of biosimilars, he said that when there is competition in Europe the price level is driven down – not just that of the biosimilar and its reference products, but that of the whole product class.

Typical price reductions for biologics with established competitors are in the 13-34% range, but in many countries price reductions can be as much as 50-70%. "Competition for the payer is a beautiful thing, and it has certainly impacted costs," he declared.

However, he said that, perhaps surprisingly, there was "very limited correlation between how much price reduction there is and what the biosimilar market share is." This is partly because originators have reduced their prices – in most cases biosimilars are bought by hospitals where originator companies are used to giving discounts – but also because in some cases the originator has launched a long-acting/pegylated version without a price premium over the short-acting products, effectively reducing price level and protecting at least some of their market share.

LESSONS LEARNED

Looking at what has been learned in the 10 years since the launch of the first biosimilars, Troein said that "no-one" would now argue that biosimilars are not as safe and effective as the reference drugs. Extrapolation of indications is now generally accepted, although further real world evidence would be needed to prove products remained effective and safe, and while most people would agree that biologic products require slightly different monitoring than small molecule drugs, "in most countries this is in place."

Switching to a biosimilar is now "fairly acceptable," particularly in hospitals, but "very few stakeholders are ready for [pharmacy] substitution," Troein said.

As for the factors that determine biosimilars' market share, experience has shown that "local champions" in hospital trusts are important in encouraging uptake of biosimilars. These "champions" will "see the whole picture, are willing to understand all the issues, help to get the physicians to do their part, and get the money allocated so that the extra work that needs to be done by doctors, nurses and so on is funded."

By way of example, he said that with infliximab, in northern European countries like Denmark, Finland and Norway, switching was recommended by rheumatologists, hospitals and/or regulators, and financial incentives were also strong in these countries. These countries also had a "very quick" conversion from originator to biosimilar, while other markets like the UK showed slower but steady growth.

As for etanercept, switching to the biosimilar (Samsung Bioepis' *Benepali*) was faster than with infliximab, Troein said. His presentation showed that uptake of biosimilar etanercept in Europe was strongly influenced by whether the drug was covered by general reimbursement of hospital tender – in Norway, for example, which has 19 counties, each with a central hospital, one month after the switch to a hospital tender, Benepali held a 65% market share in two of the 19 counties.

In the case of Celltrion's *Truxima*, a version of MabThera, which was approved in the EU in February this year, Troein said: "MabThera is typically a hospital product, one that could have a pattern that is very much what we have seen with infliximab." He noted that in Sweden more than half of MabThera use is off-label for multiple sclerosis patients, "and it will be very interesting to see how this process goes."

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Baricitinib Complete Response May Put Lilly/Incyte Behind IL-6 Blockers In RA

An FDA complete response letter seeks additional data on dosing and other safety concerns, delaying potential approval for an NDA that already had been pushed back three months. Interleukin-6 inhibitors sarilumab and sirukumab, now under review at the FDA, both could obtain approval before baricitinib.

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Eli Lilly & Co. and Incyte Corp.'s hopes to bring their oral selective JAK1/2 inhibitor baricitinib to market soon in rheumatoid arthritis were dashed by an FDA complete response letter announced April 14, potentially putting a pair of interleukin-6 inhibitors now under review by the US regulator ahead in the race to get new RA therapies approved.

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Filed for approval in January 2016, baricitinib initially had a January 2017 user fee deadline, but that was pushed back three months by the FDA to allow for additional data analysis. With the complete response letter, the drug Lilly and Incyte have partnered on since 2009 looks likely to reach market after GlaxoSmithKline PLC/Janssen Pharmaceuticals Inc.'s sirukumab and Sanofi/Regeneron Pharmaceuticals Inc.'s sarilumab, both IL-6 inhibitors.

FDA's CRL calls for additional data to determine the most appropriate dose of baricitinib and further address other safety concerns from clinical trials, which could take a while to collect.

Lilly revealed that it had received the CRL on April 14, saying that it and Incyte "disagree with the Agency's conclusions." Lilly declined to comment due to the ongoing nature of discussions with the FDA – in a release the Indianapolis pharma said timing of a resubmission depends on the outcome of those discussions.

Sanofi and Regeneron received a CRL for their Biologics License Application (BLA) for sarilumab last October, citing manufacturing concerns following a routine on-site FDA inspection of a "fill-and-finish" site in France. The sarilumab BLA at the time had an action date of Oct. 30.

Sanofi reported during a March 28 investor call that the two companies recently re-filed the sarilumab BLA. They hope for a two-month review of the resubmission for sarilumab, which gained its first approval Feb. 1 in Canada under the brand name *Kevzara*.

"This follows the FDA's classification of Sanofi's Le Trait [France] manufacturing site as acceptable after recent inspection of the facility," Sanofi CEO Olivier Brandicourt told the call. "We continue to anticipate an FDA action date for Kevzara in the second quarter of 2017, which is, of course, subject to FDA's acceptance of the resubmission and determination of a new action date."

GSK/J&J's sirukumab BLA currently is under review by FDA with a Sept. 22 action date. If Sanofi and Regeneron get the speedy review they seek for their re-submitted application, sarilumab could reach the US market first, with sirukumab now also likely ahead of baricitinib in the timeline.

LIKELIHOOD DECREASES

Biomedtracker downgraded baricitinib's likelihood of approval by 28 percentage points to 70% based on the news of the CRL April 14, which is still 11 points above average for a Phase III candidate for RA. However, the service gives sarilumab a 96% chance of approval and sirukumab a 94% likelihood.

Baricitinib's NDA was based on a five-study Phase III program, including the RA-BEAM study in which it demonstrated superiority against AbbVie Inc.'s widely used tumor-necrosis factor (TNF) inhibitor *Humira* (adalimumab) on signs and symptoms of the disease as well as on patient-reported outcomes, and the RA-BEGIN study, where it demonstrated superiority to methotrexate.

Lilly/Incyte's JAK inhibitor has earned approval in Europe under the brand name *Olumiant*, following a December 2016 endorsement by the Committee for Medicinal Products for Human Use (CHMP). It is indicated for the treatment of moderate-to-severe RA in adults with inadequate response or who are intolerant to one or more disease-modifying anti-rheumatic drugs, either as monotherapy or in tandem with methotrexate.

In an April 7 note, Jefferies analyst Brian Abrahams pointed out that Olumiant's list price has been set in Germany at approximately $1,560 for a four-week supply of the once-daily tablet or $5,316 for a 14-week supply. This pricing suggests that Lilly and Incyte intend to compete with Humira and Amgen Inc.'s anti-TNF *Enbrel* (etanercept) on price in Europe.

Baricitinib also will need to be positioned price-wise to compete with biosimilars of the anti-TNF drugs – biosimilar etanercept and adalimumab already are on some European markets and are expected soon in the US. "Anti-TNFs, either the reference brands or their biosimilars, are likely to be the preferred first-line agents based on formulary placement. Payers may enforce step therapy requiring treatment with an anti-TNF before baricitinib can be used," Datamonitor Healthcare analyst Christina Vasiliou previously told *Scrip*.

Abrahams sees the pricing as indication that, even with superior efficacy over market-leading Humira, Lilly is willing to set a modest discount to the TNFs. "We believe this suggests they are committed to making the drug highly competitive versus well-entrenched, already-discounted/contracted incumbents, which could help long-term adoption," he wrote.

In Germany, drug sponsors typically set pricing for new products in the first year on market, which is negotiated downward thereafter. Abrahams said the German pricing comes in about 15% below the already discounted cost for the anti-TNF drugs, which is lower than Jefferies anticipated. It also may suggest a similar pricing strategy will be adopted in the US, the analyst said.

COMPETING WITH XELJANZ

In both Europe and the US, baricitinib will compete not only with the anti-TNF class and potentially two new IL-6 inhibitors, but also Pfizer Inc.'s selective JAK1/3 inhibitor *Xeljanz* (tofacitinib), a sales underachiever since its US approval in 2012. The drug only obtained EU approval as an RA therapy this past January, after two previous rejections in 2013 due to safety concerns.

There has been no direct head-to-head comparison of Xeljanz and baricitinib in RA, but market analysts generally expect the newer drug to offer better efficacy. That, combined with the fact that the Pfizer drug in it is original formulation is dosed twice-daily, should give Lilly and Incyte's product some differentiation in the JAK inhibitor class. (Editor's note: While this story initially said Xeljanz is taken twice a day, a once-daily, 11 mg Xeljanz XR version of the drug was approved by the FDA in February 2016.) Datamonitor analyst Vasiliou projected peak sales of $1.9bn for baricitinib in 2025, outpacing Xeljanz, which brought in $927m during 2016 and has yet to post a blockbuster sales year.

In the larger RA competition, Regeneron recently indicated it was not inclined to try to compete on price, at least in the US. Senior Director for Health Economic and Outcomes Research Andreas Kuznik told the Institute for Clinical and Economic Review March 24 that a low price for sarilumab would be unlikely to result in high volume for the product.

"Rebates are massive in this class. And those rebates create a disincentive to compete on price," the exec said. "Regeneron and Sanofi are launching a new drug but there is very little incentive for us to price it low and compete on price because price doesn't matter. We are not going to get better access in the marketplace."

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Opdivo Turned Down By NICE In Head And Neck Cancer

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BMS looks unlikely to have a positive NICE opinion synchronized with European approval of Opdivo in head and neck cancer, after the HTA body turned down the checkpoint inhibitor in its draft appraisal.

Receiving a positive NICE recommendation at around the same time as EU approval is likely to be helpful to companies for marketing to doctors and payers, but such synchronicity has not been achieved by Bristol-Myers Squibb Co. for its checkpoint inhibitor, *Opdivo* (nivolumab) in head and neck cancer.

The National Institute for Health and Care Excellence, the UK's health technology assessment (HTA) body, issued a draft appraisal on April 11 concluding that nivolumab is too expensive to be used as an option in the UK for the treatment of squamous cell carcinoma of the head and neck in adults progressing on or after platinum-based chemotherapy.

The appraisal is being conducted relatively early, with Opdivo in head and neck cancer only receiving a positive opinion from the EU's scientific panel, the CHMP, back in March 2017; the additional indication is awaiting final approval from the EU Commission.

Although in this case early appraisal did not achieve a positive NICE result, the company has in the past gained a positive NICE opinion at around the same time as EU approval of a new indication. In June 2016, BMS gained a positive recommendation from NICE for use of the combination of Opdivo and BMS's other checkpoint inhibitor, *Yervoy* (ipilimumab), in advanced skin cancer, only weeks after the combination was approved by the European authorities.

Being judged initially to be too expensive for use in the UK but being cleared after offering a price discount has also featured in Opdivo's past: nivolumab was recommended by NICE as an option for use in previously treated advanced renal cell carcinoma in Nov. 2016, provided BMS supplied nivolumab at a price discount agreed in a patient access scheme. It was initially rejected in July 2016 by NICE because the institute felt the drug didn't offer value for money.

In the current draft appraisal, the appraisal committee estimated the incremental cost effectiveness ratios (ICERs) for nivolumab in head and neck cancer to be above the £66,000 to £75,000 range per quality adjusted life year (QALY) gained compared to other treatments. This is markedly above the range considered to be a cost-effective use of NHS resources. The committee did conclude that nivolumab was associated with an extension to life of at least an additional three months, but the ICERs were still too high to be considered cost-effective. The appraisal committee also indicated that nivolumab would be unlikely to be added to the new Cancer Drugs Fund.

The appraisal already includes a BMS patient access scheme, suggesting a revision of that scheme is being sought. Under the scheme, nivolumab would be supplied to the NHS at a discount to the list price of £439 per 40 mg vial and £1.097 per 100 mg vial.

The results of the CheckMate-141 study were used to support BMS's submission to NICE, where nivolumab was compared with the investigator's choice of therapy, but the committee concluded the long-term overall survival benefit was uncertain.

That study showed a median overall survival of 7.5 months in the nivolumab arm and 5.1 months in the investigator-choice arm. However, the median progression free survival was 2 months and 2.3 months respectively. Overall survival was double in the nivolumab arm (36%) compared with the investigator-choice arm (16.6%) at 12-month follow-up, but the overall survival benefit beyond 24 months was uncertain, the committee said.

Comments on the draft are now being sought until May 4, after which a second draft guidance will be formulated.

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ALEX Ups The Ante For Alecensa In ALK+ NSCLC

Roche's Alecensa has bested Pfizer's Xalkori in the Phase III head-to-head ALEX study in first-line non-small-cell lung cancer, making a strong case for it to be the new gold standard therapy in ALK-positive patients, in favor of Novartis's Zykadia.

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Roche 's second-generation ALK inhibitor *Alecensa* (alectinib) has shown a significant improvement over Pfizer Inc. 's first-generation product *Xalkori* (crizotinib) in progression-free survival when used first-line in advanced ALK-positive non-small cell lung cancer (NSCLC).

The top-line Phase III results come on the back of similarly positive data from the J-ALEX trial in Japanese patients which also went head to head against Xalkori, and position the Roche product as a new gold standard therapy in this setting. The two studies give Alecensa the edge over its major competitor, Novartis AG 's second-generation ALK inhibitor *Zykadia* (ceritinib) in NSCLC, despite the fact that it is closer to approval in this particular population.

Overall Zykadia had the advantage of beating Alecensa to market, being first approved in the US in June 2014, and a supplemental filing for first-line use was accepted and granted a priority review in February, but Roche is being spirited in response. It now plans to submit the ALEX data to regulators, including in the US and EU, to beef up its label (see box) and strengthen its position in the ALK+ NSCLC treatment landscape.

Both second-generation products have advantages over the current standard of care Xalkori in terms of resistance generation and their ability to cross the blood-brain barrier and act on tumors in the CNS, a common site of metastases for ALK-positive NSCLC.

Novartis reported the full data from its ASCEND-4 study in December which compared Zykadia against standard first-line chemotherapy in ALK-positive advanced NSCLC and showed a doubling of mean PFS (16.6 months vs 8.1 months) but while this efficacy was deemed decent compared with Xalkori, it was not thought good enough to overcome doctors' caution over its tolerability profile, especially with the ALEX Alecensa data in the offing.

Roche's stated aim is to "transform the standard of care" in this setting with Alecensa and now that the headline data are in, analysts are confident that its product will indeed have the advantage, even in the absence of any actual figures for the drug's performance beyond the fact that it hit its PFS primary endpoint. The J-ALEX study was stopped early in February 2016 after an independent monitoring committee noted that it met its primary endpoint of PFS, and subsequent data released in May 2016 revealed that while the median PFS was 10.2 months (95% CI: 8.2-12.0) in the Xalkori arm, the median PFS had still not been reached in the Alecensa arm (95% CI: 20.3 months-not reached).

"Details of the ALEX study will be presented at an upcoming conference, but if efficacy and side effect results mirror those seen in J-ALEX, they should position Alecensa as a best in class treatment for ALK+ NSCLC," said analysts at Jefferies. They are currently modelling around CHF720m of Alecensa sales in 2021, which they expect will be 1% of total group sales forecast in that year.

Analysts at Datamonitor Healthcare note that since Xalkori is the only ALK inhibitor approved for first-line NSCLC, it is likely a much more appropriate comparator in the eyes of physicians and payers alike than the chemotherapy used in the ASCEND-4 study of Zykadia. Dr Dustin Phan said, "This gives Alecensa an important competitive advantage over Zykadia, particularly in the US and EU, where Zykadia holds the advantage as the first second-generation ALK inhibitor to market. Although Zykadia could now be on track to be the first second-generation ALK inhibitor approved for the first-line setting in the US, Alecensa's positive data in two Phase III head-to-head trials could potentially provide it a significant boost in market share over Zykadia, establishing it as the next standard of care."

However, there is further competition on the horizon. The end of the month should see the FDA verdict on the approval of Ariad Pharmaceuticals Inc.'s brigatinib for ALK+ NSCLC in patients resistant to crizotinib – the PDUFA date is April 29. Further back is Xcovery LLC's ensartinib in Phase III.

Alecensa Quick Facts

First approved in Japan (through Chugai) in July 2014, for second-line use in the orphan indication of ALK-positive unresectable, recurrent/advanced NSCLC.

Alecensa received an accelerated approval in the US in December 2015 through Genentech Inc. (Roche) for ALK-positive metastatic NSCLC patients progressing on, or intolerant to, crizotinib. The ALEX study will be used to convert the current accelerated approval of Alecensa in people with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib to a full approval as an initial treatment.

The FDA also granted it a Breakthrough Therapy Designation for the treatment of people with advanced ALK-positive NSCLC who have not received prior treatment with an ALK inhibitor in September 2016.

In the EU, Alecensa was granted conditional marketing authorization in February 2017 for monotherapy use in ALK-positive NSCLC previously treated with crizotinib. The ALEX study will act as the post-authorization safety study to convert this into a full approval.

Alecensa is approved as a monotherapy for people with ALK-positive NSCLC who have progressed or are intolerant to crizotinib in nine other countries.

ALEX DETAILS

The ALEX study randomised 303 treatment-naïve patients from 31 countries with ALK-positive NSCLC (as determined by Roche's VENTANA ALK (D5F3) CDx Assay) to receive either Alecensa or crizotinib. The primary endpoint of the ALEX study PFS as assessed by the investigator and secondary endpoints include: Independent Review Committee (IRC)-assessed PFS, time to central nervous system progression, objective response rate (as defined by RECIST criteria), duration of response, overall survival, health-related quality of life and safety.

The safety profile of Alecensa was consistent with that observed in previous studies, with no new or unexpected adverse events, Roche said.

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CONTINUED FROM COVER

cell carcinoma of the lung whose disease has progressed on or after treatment with platinum-based chemotherapy.

Stephen Doyle, vice president and head of the Specialty Care business unit at Boehringer Ingelheim China, said at a press conference in Guangzhou that Boehringer had been working closely with the Chinese Society of Clinical Oncology for a few years to support the development of Giotrif in the country. A large Chinese patient population was involved in the LUX-Lung clinical trial study, with 43 Chinese hospitals participating in the international program, he noted.

"Currently the imported [Giotrif] drugs are under customs and sample testing. We hope to officially launch the drug into the market before July," said Doyle. "We will think of some innovative ways to deliver the drug to patients, in addition to traditional channels of oncology hospital and pharmacies next to the hospital."

MEDICAL NEEDS

The rapid review and approval of the two lung cancer drugs signal an urgent need for new, targeted treatments with the potential to address specific types of cancer with high incidence and significant unmet medical need in China, and a potentially large market.

According to the latest data from the Chinese Society of Clinical Oncology, lung cancer is the leading cause of cancer death among both men and women in the country, with a continuously increasing incidence rate. China now logs more than 730,000 new cases of lung cancer yearly, of which 80-85% is NSCLC. Most patients are already at a late stage when they are diagnosed, with an average survival period of 12.9 months. The overall three- and five-year survival rates are 19% and 11%.

Patients who have the EGFR mutation form of NSCLC, which occurs in 30-40% of NSCLC patients in China, are particularly sensitive to treatment with currently available EGFR-TKIs, which block the cell signaling pathways that drive the growth of tumor cells.

Three new targeted drugs were already available in China for NSCLC. AstraZeneca's *Iressa* (gefitinib) was launched in 2004, while Roche's *Tarceva* (erlotinib) came onto the Chinese market in 2007. The third novel targeted drug, Zhejiang Beta Pharmaceutical's *Conmana* (icotinib), for patients with EGFR mutations, became available in 2011.

According to a research note from the China International Capital Corporation, the market size of small molecule targeted drugs for lung cancer reached CNY3.23bn ($468m) in China in 2015, with a compound annual growth rate of 23%. Iressa held 39% of the market for EGFR-TKIs.

PRICING, STRATEGY

"EGFR-TKI drugs have been used in Asia for more than a decade, China alone has around 100,000 users every year. Hence, it has accumulated a large patient population with TKI resistance, which provides opportunities for the new generation of TKIs," said medical marketing expert Qian Liu.

Liu estimated that the price of Tagrisso in China would be similar to the drug's cost in Hong Kong and Taiwan, which is around CNY60,000 to CNY70,000 ($8,690-10,138) per month and could make it the most expensive oral drug in the country.

"This is an important step forward for Tagrisso and a significant opportunity to bring a breakthrough medicine to patients with NSCLC in China, where EGFR mutation rates are some of the highest in the world," said Sean Bohen, Executive Vice President, Global Medicines Development and Chief Medical Officer at AstraZeneca.

But Liu said it is also important that the patient's EGFR T790M mutation status be determined through a validated test using either tumor DNA derived from a tissue sample or circulating tumor DNA from a plasma sample.

Taking a different approach, Boehringer is collaborating with Xiamen-based Amoy Diagnostics, a company focused on molecular diagnostics for oncology precision medicine and developing EGFR testing kits, according to Doyle.

"Boehringer is active in talks with China healthcare authorities for possible reimbursement, while working with charity organizations, with the aim of helping more patients to get access to Giotrif," the executive added.

"It is encouraging to see [other] targeted NSCLC drugs entering the national reimbursement list," Doyle continued. "Boehringer is trying to bring Giotrif onto provincial reimbursement lists first. Before entering reimbursement lists, we will work with charities to establish a patient assistance program for the poor."

Doyle added that Boehringer would soon develop a pricing strategy for the Chinese market.

Giotrif, even as a second generation EGFR-TKI, would still have an opportunity in China, said Yilong Wu, president of the Chinese Society of Clinical Oncology. "The third-generation of EGFR-TKIs is aimed at a selective population, we have to do the genetic testing to find out the drug-resistant mutation," Wu observed. "Because of this indication, it is clear that the third-generation EGFR-TKI is definitely used after the first or second generation treatment fails."

Wu said that the society was still waiting for research results by the end of this year or early next year to evaluate if third-generation EGFR-TKIs can be used directly in patients who have not received first or second generation EGFR-TKIs.

PRICING PRESSURES

However, the growing medical demand and availability of new drugs are leading to increasing health budget pressures in the lung cancer sector. In May of last year, health authorities announced price cuts of more than 50% for three drugs, including Iressa, for which the monthly cost was slashed from CNY15,000 to CNY7,000, while that of Conmana dropped from CNY12,000 to CNY5,500.

The monthly cost of Tarceva was also cut by 30% in 2016, falling from CNY18,400 to CNY12,880.

In a further move to provide wider access to affordable medicines for disease including cancer, kidney disease, hepatitis and hemophilia, the Chinese government overhauled the National Reimbursement Drug List in January 2017 by adding more than 300 new and traditional drugs, including Iressa and Conmana.

In another challenge to Iressa, the first locally made generic version has recently hit the market in China. The product, Yiruike, was produced by Qilu Pharmaceutical Co. Ltd. and approved for marketing following the expiry of the original drug's Chinese patent in April 2016. It is sold at less than CNY2,000 a pack, a fraction of the price of the branded product..

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From the editors of *PharmAsia News*.

Is The Microbiome Hype Or Happening?

JESSICA MERRILL & LUCIE ELLIS

Buzz is growing over the potential of research on the microbiome to yield new therapeutics. Scrip asked pharma, academics and venture capitalists how long it might take to see results, what breakthroughs are needed and which therapeutic areas might benefit first. Vote to tell us what you think.

Research is exploding around the microbiome, the trillions of microbes living in and on the human body, as a means to address a range of diseases. Academics are conducting early research, VCs are backing microbiome-focused start-ups and even big pharma is waking up to the potential for new therapeutics based on manipulating the microbiome.

But the reality is there is a lot to be sorted out when it comes to understanding how the microbiome works, how changes in microbiome impact disease and how therapeutics can be developed that target the microbiome – and how those can be made into commercially viable, patent-protected drugs.

Scrip asked a range of industry experts, from academics to venture capitalists to start-up executives and big pharma researchers, what they think about the status of microbiome drug development and the biggest challenges facing the field of research. The result is that while most people *Scrip* talked to think the microbiome presents enormous opportunity, the challenges remain daunting.

Vote to tell us what you think and see below for the results of our last Scrip Asks reader poll.

HAVING THEIR SAY:

Big Pharma: *Johnson & Johnson, Pfizer Inc.*
Start-Ups: *Synlogic Inc., RedHill Biopharma Ltd., SkinBioTherapeutics*
Venture Capital: *Atlas Ventures, Flagship Pioneering*
Academic Institutions: *University of California, San Diego; Sanford Burnham Prebys*

Dirk Gevers, Global Head Of The Janssen Human Microbiome Institute

It's happening! The increased focus on the microbiome over the past decade is already starting to result in multiple products that are under clinical development today, and


Dirk Gevers

could result in products on the market in the not too distant future. Several companies are undertaking clinical trials, including some in Phase II and III, to evaluate products that use a microbiome-based approach to tackle [gastrointestinal (GI)] infections with Clostridium difficile.

If one looks beyond purely therapeutics, we find DayTwo offering a personalized nutrition solution based on your gut microbiome aiming at improved glucose control. In addition, MicroBiome Therapeutics LLC completed their study aimed at diabetic dysbiosis and has stated that it's targeting to be available in 2017. Behind these pioneers, we see a strong ecosystem of entrepreneurs pursuing a wide range of product types and unmet needs, holding a promise for many more solutions to follow.

That said, in terms of the potential to deliver products to patients, it is still a young field, and there is still much to learn about how we can harness the microbiome to inform new types of health solutions. We believe the microbiome field is ripe for innovative collaboration models that go beyond traditional in-licensing and investments. We need members of the community to work together and bring their specific expertise, be it in early-stage research, R&D, analytics or manufacturing. A robust community of microbiome innovators working together is going to be critical to effectively translate promising microbiome science into solutions that ultimately address the root cause of disease and promote health.

Nikola Trbovic, Director R&D Technology Strategy, Genome Sciences & Technologies, Pfizer

The human (gut) microbiome has a range of potential therapeutic applications. Live biotherapeutics, also colloquially referred to as "bugs as drugs", as well as bacterial metabolites that mediate relevant host-microbiome interactions are among the most advanced therapies in development and may well be among the first approved microbiome therapeutics. However, in addition to the fundamental questions of efficacy and safety, a number of challenges related to manufacturing, IP, and designing a clinical and regulatory path remain to be resolved.


Nikola Trbovic

A different approach is to identify host or bacterial targets that mediate host-microbiome interactions and use established therapeutic modalities (e.g., small molecules) to drug them, making drug design more straightforward but requiring deeper understanding of the underlying cellular and molecular mechanisms. In addition, the microbiome can also serve as a biomarker for disease progression and drug response to inform precision medicine approaches to treating disease.

One of the biggest questions in translating human microbiome research into therapeutics is whether the observed dysbiosis causes disease or is a symptom thereof. It is one of the main reasons why the vast majority of advanced therapies in development are going after either C. difficile infection or inflammatory bowel disease (IBD): the former is a dysbiosis of the gut microbiome, and the latter is a disease

of the gut with some evidence for causation. That said, intriguing associations have been shown in a wide range of diseases, including obesity, rheumatoid arthritis, (immuno-)oncology and neurological diseases like Parkinson's, and further research into the underlying mechanisms will help improve our understanding of the role of the microbiome in these diseases.

At Pfizer, we are tremendously excited about the promise of the human microbiome in treating disease. Given the many outstanding questions, our efforts are focused on applying our core capabilities to microbiome profiling for precision medicine, as well as to understanding the mechanisms of host-microbiome interactions to identify targets for conventional drug development. We also see the immediate potential in IBD and auto-immune diseases, but at the same time we are exploring potential applications in metabolic diseases, immuno-oncology and neurology.

Bruce Booth, Partner, Atlas Ventures

Bruce Booth

The exploration of the microbiome as a therapeutic focus, like any new area, has followed the Gartner hype cycle [a way of looking at the maturity and adoption of technologies]. Over the past few years, we've seen enormous interest in the field, and some rather incredible claims – the peak of the cycle. But making microbiome-directed drugs will be much harder, as clinical development and therapeutic intervention in or with the microbiome is challenging.

That said, I do think we'll see therapies developed in conditions like C. diff. in the coming years. Broader chronic diseases, like obesity, have been plagued by spurious microbiome correlations and low signal-to-noise noise, and will likely require more time for the science to mature.

David Berry

David Berry, Partner, Flagship Pioneering

The microbiome has rapidly emerged as one of the most interesting areas of science and therapeutic development. The good news about the microbiome is we have already seen results and know that the microbiome should be important to treat disease. This comes from the work over the past several years using microbiome transplants – better known as fecal transplants.

The challenge, however, is because of their heterogeneity and the fact that they have been shown to transmit everything from viruses to obesity to food allergies, they are not the substrate to become drugs. Companies like Seres Therapeutics Inc. and Evelo Biosciences have been leading in the charge to make microbiome therapeutics into drugs, and are lining up for important data to emerge in the next couple of years. Their focus on manufacturing issues is essential to making viable microbiome drugs – a challenge that has stymied many. Data will be emerging on infectious disease (particularly Clostridium difficile infection), ulcerative colitis, cancer and systemic immune diseases.

Rob Knight, Director of The Center for Microbiome Innovation, University of California, San Diego

There are already people alive now who would be dead had they not received microbiome transplants for C. difficile. So microbiome therapies are the present, not the future. But the question is how general these therapies will be. Will they work for many diseases, as antibiotics have transformed our relationship to infections, or will they be limited to a few specific diseases? Think of the difference between snake oil as a general cure-all versus captopril isolated from snake venom as the first commercial ACE inhibitor. Will they only work for specific people, as antidepressants and anticancer agents do? And how can we separate the hype from the reality?

At UC San Diego's Center for Microbiome Innovation, we bring together clinicians, computer scientists, pharmacologists, ecologists and many other disciplines to address these hard problems. We are taking a two-pronged approach: (1) short-term targets with high promise such as using microbiomes to stratify patients for treatment, or using FDA-approved drugs to hit targets in the microbiome, and (2) developing the next generation of microbiome tools, including better technical readouts of who is in a microbiome and what they are doing, integration with immunology, physiology, nutrition and neuroscience on the host side, and an unprecedented database of microbiome and metabolome samples through American Gut, the Earth Microbiome Project, and our various government-, company-, and philanthropically-funded projects.

> Microbiome therapies are in use today, but their application needs to be understood –are they 'snake oil as a general cure-all [or] captopril isolated from snake venom?'

Most importantly, we are building a superb cohort of students and postdocs trained in this uniquely interdisciplinary view of microbiome science and poised to tackle the most challenging microbiome problems on scales from our bodies to our planet.

Scott Peterson, Professor, Sanford Burnham Prebys Medical Discovery Institute

The microbiome is for certain both hype and happening. It will take more time to determine just what is hype and what is

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for real, but all indications suggest that it is more happening than hype. Remarkably, the reach of the microbiome in terms of human health clearly extends well beyond the gut.

The therapeutic benefits of microbiome-based "drugs" will come in two phases, the first based wave will be represented by improved probiotics that are GRAS [Generally Recognized As Safe] and therefore do not need FDA approval. Similarly, prebiotics are likely to have major impact in the near term so long as companies can find ways to protect inventions and make such supplements profitable. The next big push in probiotics will require advances in encapsulation technology to improve the delivery of live bacteria to their site of action.

JC Gutiérrez-Ramos, CEO Synlogic

I think the microbiome is going to be a key component of how we treat diseases in the future. I personally don't believe it has been hyped at all. It's the reason I left big pharma and came to lead a company that operates from the microbiome. I believe that it is a very important area.

JC Gutiérrez-Ramos

Of course, the detail is the one that we have to work out, particularly as we develop drugs. I'm in the camp [that] there is absolutely no debate about the importance of the microbiome in human health. The question is how do you harness it to make medicines. There are many companies at the moment that are trying to understand that complexity. There are different approaches that are being used, and some of them will work, some of them will work in 10 years, some of them we hope with more focus, will work in less than 10 years.

The areas that could be first, one is inflammatory diseases, another one is metabolic diseases and the third one is rare genetic disorders. These are the three. The connection between the human gut and the brain is one that is being more and more documented, but to develop drugs for the brain is complex by itself, so I don't include them right away. Applications to cancer, adjuvant therapies might develop, but you have to be very aggressive.

One thing that is very close to our heart and why we are focusing so much [attention] is manufacturing, as you get into complex mixtures of bacteria. This is one area we have to watch for. The second thing is dose response and pharmacology. For this new class of drugs, drugs that operate from the microbiome, to be understood, to be used by physicians, to be adopted by pharma, basic pharmacology and dose responses that we are used to have to be brought to the field. This is another area where we are investing a lot of time and effort to really characterize the potency of our synthetic biotics.

Catherine O'Neill, CEO SkinBioTherapeutics and Professor, University of Manchester

It's definitely happening. Scientists studying the gut have demonstrated that disturbance to the gut microbiome is a potential cause of disease. The research effort also appears to be showing a translational effect around the body; in other tissues, there is not only a link between an organ's own microbiome, but also the gut microbiome and disease. The problem facing us now is how to harness the vast amount of research data into the creation of new therapies.

Catherine O'Neill

The best example currently is the use of fecal transplantation to help severe antibiotic-associated diarrhea. This has proved remarkably successful. Other therapies are starting to emerge but there is some way to go. This is partly because the microbiome is vast in terms of types of bacteria. Whilst offering a lot of promise, it will take some time to ascertain which aspects of the microbiome will be most useful and how best to harness it. Our approach at SBTX has been top use a bacterium that is already well characterized and see if it can offer similar benefits when applied to skin.

Ira Kalfus, Medical Director, RedHill Biopharma

The microbiome is very real. These bacterial cells and viral and other microbial organisms are increasingly recognized for their role in normal human physiology and in disease states (dysbiosis) such as obesity, diabetes and metabolic disease. Advances in our understanding of the microbiome portend to new potential therapies for diseases characterized as autoimmune in nature as well. However, much of this experimental research is early and expected to take many years to yield clinical applications.

RedHill Biopharma takes a slightly different approach to the microbiome. Clinicians believe that bacteria play a significant role in human disease and that, in most cases, the appropriate treatment involves eradication of pathogenic bacterial infection. In rare instances, this may involve replacement of pathogenic organisms. RedHill is developing two therapeutic agents in the microbiome space, both currently in Phase III of development. Much like streptococcal infection causes pharyngitis and potentially rheumatic heart disease, and H. pylori causes peptic ulcer disease and gastric cancer, gut pathogens are putative causes of other disease that have been considered autoimmune in nature.

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Poll Results From Our Last Scrip Asks…
Will orphan drug pricing come under more pressure over the next five years?
http://bit.ly/2pao4Vr

Neurocrine Beats Teva To Tardive Dyskinesia Market With Ingrezza

JOSEPH HAAS joseph.haas@informa.com

Neurocrine secured FDA approval for the first drug to treat tardive dyskinesia, a large market that crosses multiple diseases and has blockbuster potential.

Neurocrine Biosciences Inc. has secured an important head start over rival Teva Pharmaceutical Industries Ltd. for the launch of *Ingrezza* (valbenazine), an elective vesicular monoamine transporter 2 (VMAT2) inhibitor approved Apr. 11 for the movement disorder tardive dyskinesia (TD).

The category is expected to be a competitive one with blockbuster potential, and Neurocrine may not have a substantial lead over Teva, which has its own VMAT2 inhibitor *Austedo* (deutetrabenazine) pending at the FDA for TD, with an Aug. 30 action date.

Pricing and rebates could present a competitive dynamic for differentiating the products. Neurocrine did not say precisely how it will price Ingrezza, only that it will be priced competitively. The San Diego biotech said it will release the price when Ingrezza launches on May 1.

Neurocrine and Teva have been engaged in a neck-and-neck battle to get the first drug approved in the US for TD. Ingrezza crossed the finish line first as scheduled on April 11, but Teva's Austedo could be right behind. In addition to the indication pending at FDA, Austedo was already approved by FDA on April 3 for chorea associated with Huntington's disease. The indication in TD is the larger opportunity because the movement disorder effects patients across a range of illnesses; Teva has said there are about 500,000 patients in the US with the condition.

Both drugs are VMAT2 inhibitors, but there are differences between them. Neurocrine's drug is an internally developed novel compound, while Teva's is a deuterated formulation of Lundbeck Inc.'s *Xenazine* (tetrabenazine), approved for but not widely used in Huntington's chorea because of a poor safety profile.

It appears Neurocrine will enjoy not only a first-to-market edge, but also a cleaner label in TD, as it was approved without any black box warning on safety. Austedo's label for Huntington's chorea includes a black box warning for risk of depression and suicidality, similar to that contained in the Xenazine labeling, though language in other parts of the label suggest improvements.

On an April 11 investor call, Neurocrine executives noted that their label includes no black box warning, no contraindications, and a clear and broad indication. Ingrezza is approved to treat all adults with TD, with warnings for risk of somnolence and QT prolongation.

Investors were pleased with the timely approval and label; the stock surged 24% to close April 12 at $51.80.

TRANSPARENT PRICING

Austedo is priced at a wholesale acquisition cost of $60,000 per year, based on a therapeutic dose of 24 mg daily, Teva has said, although actual pricing will vary because the drug is titrated. The Israeli biopharma is measuring this price against the $90,000 WAC for a 50 mg dose of generic tetrabenazine.

By contrast, Ingrezza is approved as a 40 mg tablet, with labeling recommending that patients start on a 40mg daily dose and increase to 80 mg after one week. The simpler dosing should also result in more transparent pricing of Ingrezza. Asked on the call if the variability in pricing for Austedo – although not yet approved for TD – had impacted Neurocrine's pricing strategy for Ingrezza, president and chief operating officer David-Alexandre Gros said the company has not changed its prior pricing guidance of $20,000-$60,000.

Gros also discussed how Teva might price Austedo for TD and what Neurocrine makes of that possibility.

"One would estimate that the cost for treatment of typical patients [for Austedo] with regards to Huntington's disease would be somewhere between $90,000 to $120,000 a year," the exec said. "So, if we look at their studies in TD and we assume a per-milligram pricing structure, then we'd anticipate that the average cost for patients with TD [would] range somewhere between the $60,000 to $90,000 marks annually. And looking at that and at that range, we intend to be competitively priced."

CEO Kevin Gorman reiterated during the call the great challenge Neurocrine has underlined in preparing the market for the first approved drug therapy for TD, noting that physician education efforts have been underway for approximately one year. This ongoing process is part of the reason why the biotech decided to delay announced the pricing of Ingrezza, he said.

"In terms of the price, what we wanted to do was to announce the pricing environment where we'd be fully able to articulate the value of our medicine to all the stakeholders," Gorman explained. "And as such, we felt that it would be important to do so once we're going out and fully commercializing."

Neurocrine also stressed on the call that its priority is to make Ingrezza accessible for all patients who are prescribed the drug, and that it intends to price 40 mg and 80 mg formulations of the tablet at par so that physicians can determine the best therapeutic approach for their patients with worrying about cost. It is offering a START program to provide the drug to patients free of charge while reimbursement is worked out with insurers.

INGREZZA'S SLOW LAUNCH

In an April 11 note on the approval, Leerink Partners analyst Paul Matteis projected an annual net cost of $45,000 for Ingrezza, or $60,000 before discounts and other adjustments. Matteis reiterated a rating of "outperform" for Neurocrine's stock and called the approval and label "a best-case scenario" for Neurocrine.

That said, Leerink predicts a slow start out of the gate for Ingrezza because it is not part of a "protected class" of drugs that typically qualify for fast formulary reviews by private payers. He anticipates that reimbursement will occur steadily over nine to 12 months.

Sales revenue should be modest during the second and third quarters of 2017,

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Matteis added, despite Leerink discussions with doctors who treat patients with TD, which showed an indication to prescribe VMAT2 inhibitors quickly for patients already diagnosed with TD. The clean label with no black box warning likely could tilt prescribers further in Neurocrine's direction, the analyst added, since there is virtually no anticipation that Austedo will get as clean a safety label if it is approved for TD.

Consensus estimates for 2017 sales of Ingrezza are around $15m, but Leerink is projecting roughly $11m, due to its expectations for slow reimbursement progress.

Neurocrine's planned May 1 launch, a month earlier than previously indicated, will draw on a sales force of 160 reps and regional managers, chief commercial officer Eric Benevich said. The company has received more than 8,700 applications for these positions, and the force will average about 15 years of sales experience in the neurology or psychiatric settings with the vast majority having worked on at least one previous launch.

The biotech has been focused on increasing awareness of TD and how Ingrezza might help patients for the past year through its Take On TD initiative, Benevich added. This effort has been expanded to include content directed toward TD patients and their caregivers, he said.

Typical of a specialty drug, the sales force will focus on a specific priority group of prescribers. "Recently, we developed an initial call list of physicians, consisting primarily of psychiatrists who manage the patient populations at risk for TD, as well as neurologists who specialize in movement disorders," Benevich said. "We will also be calling on other health care professionals such as advanced practice psychiatric nurses that care for patients in community mental health care centers across the country."

Ingrezza will enter the supply channel next week via a select pharmacy network that has been contracted to dispense the drug. Neurocrine adopted this approach due to "the unique needs of TD patients spanning varying sites of care and being managed across multiple physician specialties," Benevich said. Patients also will receive assistance with copayments and other aspects of fulfilling prescriptions through a support service hub called INBRACE, he added.

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PhRMA Keeps Focus On Industry's Reputation For Innovation

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PhRMA CEO Stephen Ubl visited Allergan's Irvine, Calif. R&D and manufacturing campus as the trade association continues its "Go Boldly" campaign promoting biopharma innovation in an effort to counteract the hit the industry's reputation has taken from drug pricing concerns.

The early stand Allergan PLC CEO Brent Saunders took in pledging to cap annual price increases combined with the specialized R&D and complex manufacturing at Allergan's Irvine campus made the Southern California site an ideal backdrop for Pharmaceutical Research and Manufacturers of America President and CEO Stephen Ubl to drive home PhRMA's message about the investment required for innovation and review its policy initiatives on drug pricing.

A recent visit to the site by a handful of journalists, Allergan execs and Ubl was intended to showcase the specialized skills and magnitude of innovation required to develop and mass-produce new medicines. Allergan's Irvine campus and the people who work there exemplify the scientists and medical advances that PhRMA has put on display in its "Go Boldly" advertising and public awareness campaign, which it kicked off earlier this year to counter the industry's declining reputation based on numerous drug pricing controversies.

Individual companies have responded to the public outcry with promises to keep annual drug price increases at reasonable levels as they balance profitability and the need to fund R&D for new products with the public relations blows when they set eye-popping list prices for new medicines and raise the cost of established therapies. Allergan's Saunders was the first to step forward in 2016 with a pledge – the company's "social contract" with patients – to keep annual drug price percentage increases in the single digits while still investing in new medicines.

Continued political pressure on pricing has made the issue a primary focus for PhRMA and industry leaders. For its part, PhRMA has commissioned research to highlight the share that pharmacy benefit managers (PBMs) take out of prices. Other research has taken aim at industry's claim that higher prices in the US go toward supporting R&D costs.

Shutterstock: Pressmaster

INNOVATION'S HIGH PRICE TAG

Ubl took the helm at PhRMA barely more than a year ago and since then has taken tours of at least 20 member companies' R&D sites to learn more about the science going on in those labs. He visited Allergan's Irvine R&D hub, which occupies an entire city block, in early April.

The company acquired the Southern California facilities when Actavis bought Allergan Inc. for $66bn in 2015 and changed its name to Allergan PLC, reflecting the combined operation's focus going forward on brand name therapies.

The Irvine campus was established in 1971 and its most recent expansion was completed in 2010. The site is where about 1,500 of Allergan's more than 2,000 California employees work, including 800 people who research and develop small molecules and biologics for the company's eye care, neuroscience and dermatology/medical aesthetics franchises. They are building on the company's biggest blockbuster, *Botox* (onabotulinumtoxinA), and novel aesthetic medicine approaches, as well as working on next-generation treatments for eye diseases and neurolog-

ical conditions and ways to manufacture those complex products.

The Dublin, Ireland-headquartered firm keeps its R&D pipeline active in these areas and four other key therapeutic areas – gastroenterology, urology, anti-infectives and women's health – largely by licensing and acquiring external assets through an "open science" model.

"We are agnostic to where the good ideas and technology comes from," Daniel Gil, Allergan's vice president of translational science, said while leading a tour of the company's research and manufacturing facilities. It's a sentiment that's repeated often by Allergan executives, including CEO Saunders, who serves on PhRMA's board of directors. Scientists at the Irvine site support many R&D programs licensed or acquired by the company, providing support on an as-needed basis.

"We have some internal projects, but most of our pipeline comes from the external world through partnerships, collaborations and licensing," Allergan's Chief R&D Officer David Nicholson said during a Q&A session with PhRMA's Ubl. "When we bring the projects in, our doors and windows are still open. We don't internalize things and say, 'Now we own this and everything has to be done our way.'"

All pharma companies expand their R&D pipelines through acquired and licensed assets, but most do it to a lesser extent than Allergan.

"We're at the extreme end of the open science spectrum. That is, we're rather unique in building our pipeline more or less solely through these interactions," Nicholson said. "In the future, our pipeline will be massively skewed towards agents that come from the external world."

Eye care, Allergan's biggest product category in terms of R&D and sales, already is growing largely through transactions that were executed to gain technology that diversifies the product offerings marketed to ophthalmology customers, including drugs, devices and surgical procedures.

One of many R&D programs highlighted during the tour at Allergan's Irvine campus was the company's sustained-release version of the glaucoma drug bimatoprost, which is delivered via a tiny implant in the eye that gives a continuous dose of the medicine for up to six months. The technology is designed to improve adherence with prescribed dosing for patients who have a hard time with traditional eye drops to treat glaucoma and often discontinue treatment.

It's a platform that Allergan hopes to use for multiple ophthalmology products, but it requires highly specialized formulation and manufacturing, which the company claims cannot be done anywhere other than its Irvine campus.

"Many of these operations are one of a kind and this is the only place where we can do this work at this scale," Vice President-Manufacturing Loren Wagner said. Asked where he finds the people to do the specialized work, Wagner said he taps local universities and other sources, and when he finds them he does everything he can to hang on to those employees, given the time and expense involved in training people to do that kind of work.

> 'In the future, our pipeline will be massively skewed towards agents that come from the external world'

R&D INVESTMENTS

The investments that Allergan and other biopharma companies make in people, equipment and facilities around the globe to support the research, manufacturing and sales of medicines – and the high number of R&D programs that fail – play a big part in the high cost of prescription drugs. At least, that's what PhRMA is trying to explain to consumers through its "Go Boldly" campaign and communications with President Donald Trump, who criticized the industry in January for "getting away with murder" when it comes to drug prices.

Ubl said PhRMA and its members "found common ground on a high level" with the newly elected US president on issues such as tax reform, international trade agreements and modernizing the FDA when he and several biopharma executives met with Trump at the end of January. Asked whether the industry can find common ground with the Administration on drug pricing, he said PhRMA is "productively engaged" with the president's staff on the issue.

PhRMA has blamed the negative attention directed at the industry during the past few years on companies like Turing Pharmaceuticals AG and Valeant Pharmaceuticals International Inc., which bought or repurposed older drugs and instituted extreme price increases. The industry also has put pressure on payers, including pharmacy benefit managers (PBMs), to more directly deliver rebates negotiated between drug makers and PBMs to patients, including through PhRMA's "Share the Savings" campaign launched on April 6.

Ubl said there are five policy issues related to drug pricing that the industry could work on with Congress and the Trump Administration in a productive way:

1. FDA modernization to make the agency more efficient;
2. Regulatory changes that allow for faster approvals of complex generics;
3. Removing regulatory barriers that get in the way of outcomes-based contract negotiations with payers;
4. Requiring payers to pass negotiated rebates and discounts on to patients; and
5. Trade agreements that protect biopharma intellectual property overseas.

PhRMA also has been engaged in discussions with Congress about Obamacare reform, but Ubl said the organization has not taken a position on legislation that might dismantle the Affordable Care Act, mainly because it's early in a long process to repeal or reform the law. PhRMA was deeply involved in the development of the ACA, which has provided health care to more than 20 million people.

Despite PhRMA's reluctance to take an early position on repealing or replacing ACA, Ubl said he's tried to take a proactive approach on issues important to the biopharma industry, such as the five policy issues he outlined in relation to drug pricing. PhRMA has tried to "develop pragmatic policies and advocate for them as opposed to listing what we're against, he said. "The ['Go Boldly'] ad campaign is designed to better tell our story – the real researchers and scientists and the patients who've benefitted from our products talking about the dramatic impact [the industry has] had on their lives."

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AACR In Review: IDO Pushes Ahead, CTLA-4 Combo Lags Behind

Though momentum is building for IDO/PD-1 combos, it's still early days for new immunotherapy programs. Clinicians and investors weigh in on the latest data from the American Association for Cancer Research meeting and the state of the immuno-oncology field.

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Merck & Co. Inc. arguably got a leg up in its bid to lead immuno-oncology coming out of the American Association for Cancer Research meeting, between the rise of IDO as a target and new data showing disappointing efficacy for Bristol-Myers Squibb Co.'s CTLA-4/PD-1 combination in melanoma compared to PD-1 monotherapy. But development activity is intense and it's unclear where it will all end.

At this year's AACR annual meeting, held April 1-6 in Washington D.C., Bristol reported that its *Opdivo/Yervoy* combination was superior to the CTLA-4 inhibitor Yervoy (ipilimumab) alone in terms of overall survival (OS) in the Phase III CheckMate 067 study in metastatic melanoma. The data should support converting the accelerated approval to full FDA approval, a win for Bristol. But the data also raised questions about whether performance of Opdivo/Yervoy compared to the PD-1 inhibitor *Opdivo* (nivolumab) as a monotherapy are good enough to justify the high toxicities associated with the combination.

In the trial, median OS at the two-year mark was 64% for the combination versus 59% for Opdivo monotherapy and 45% for Yervoy alone. The Grade 3/4 adverse event rate for the combination regimen was 58% vs. 21% for Opdivo monotherapy and 28% for Yervoy.

"That becomes the issue when staring at the survival outcome. Is the small observed difference in overall survival worth the magnified, multiplied toxicity experience with that regimen?" Keith Flaherty, director of developmental therapeutics at Massachusetts General Hospital, said in an interview at the meeting.

TURNING TO TESTING

Exploratory analyses suggest that the combination performed better in those with lower levels of PD-L1 expression – the combination was similar to monotherapy with a cutoff of 1% PD-L1 – and who were BRAF-mutant.

That suggests it may be possible to select patients for treatment based on subsets. PD-L1 hasn't been an important biomarker in melanoma in the past, but the '067 data have raised its profile.

Prescribers are now more likely to have PD-L1 testing done in a patient where the decision about whether to get the combination or monotherapy is borderline, Michael Atkins, deputy director of the Georgetown-Lombardi Comprehensive Cancer Center, said after the meeting. They also are more likely to consider studies with a PD-1 inhibitor and another agent, particularly for PD-L1-positive patients, said Atkins, who is also co-chair of the scientific advisory committee for the Melanoma Research Foundation.

Having a regimen that works in the notable subset of PD-L1-low patients would be valuable, but with about 315 patients per arm in the three-arm trial, the CheckMate 067 study wasn't actually powered to show a difference in overall survival in the subsets. Royal Marsden Hospital's James Larkin, the lead investigator of the trial, was reluctant to draw conclusions for patient management based on the subset figures, despite repeated questions at the meeting.

Flaherty said that he would like to see more data on how the combination works in PD-L1-low patients.

In the meantime, in the frontline setting, patients may choose PD-1 monotherapy or a clinical trial of a combination including PD-1 antibodies with novel agents instead, he suggested.

"PD-1 antibodies plus novel treatments is the most popular clinical trial category, not just for melanoma but lung cancer and many other cancer types," he commented.

Trials are in high demand and patients are very enthusiastic about pursuing them, Flaherty added.

According to the Trialtrove database, some 2,927 oncology immunotherapy trials are ongoing, of which 1,472 are combination studies. Bristol has the largest number of ongoing overall IO studies (377) followed by Merck (266), but in terms of agents, Merck's Keytruda is involved in the most studies compared to Opdivo 255 vs. 203 for Opdivo, according to this database.

INTEREST IN IDO

The combination of inhibitors of indoleamine 2,3-dioxygenase 1 (IDO1) and PD-1 in particular had a high profile at this year's AACR meeting. NewLink Genetics Corp. released Phase II safety and efficacy data for its IDO inhibitor indoximod with Merck & Co. Inc.'s anti-PD1 *Keytruda* (pembrolizumab) and Bristol aired Phase I combination safety data for its IDO inhibitor BMY-986205 with Opdivo.

Both datasets suggested the IDO/PD-1 combination is well tolerated, complementing data already released for Keytruda with Incyte Corp.'s epacadostat, the most advanced IDO inhibitor in development, and whetting the appetite of investors. Separate to indoximod, NewLink has another IDO inhibitor called GDC-0919 that is partnered with Roche, in Phase I.

In melanoma, Atkins notes that if nivolumab monotherapy as a frontline treatment has a 60+% survival rate in PD-L1+ patients, it will be hard for another combination to beat. Furthermore, the regimen may change to improve tolerability. In the trial, dosing for the combination included 1 mg/kg of Opdivo with 3 mg/kg Yervoy, followed by Opdivo 3 mg every two weeks.

Atkins said that the toxicity with Opdivo/Yervoy is manageable and may help prevent the need for a salvage treatment after PD-1 monotherapy for many patients.

LESSONS FOR LUNG CANCER?

Roy Herbst, a lung cancer expert and chief of medical oncology at the Yale Cancer Center, noted that there were many fewer events than expected in the CheckMate 067 study, which means it is too early to make a call about overall survival, but speaks to how

well the therapies worked, both monotherapy and combination regimens.

The patient populations and dosing regimens for the combination in the crucial indication of first-line non-small cell lung cancer vs. melanoma are different so read-through from one indication to the next is limited.

Bristol's CheckMate 227 first-line NSCLC study tests 1 mg/kg Yervoy with 3 mg/kg Opdivo, the reverse of '067, and tolerability is better. PD-L1 status has also been a more significant biomarker in lung cancer.

However, speaking generally about nivolumab/ipilimumab, Howard (Jack) West, medical director of thoracic oncology at the Swedish Cancer Institute in Seattle, commented that there is reason to be dubious about the combination based on the challenging toxicity profile of the combination overall, particularly in the community setting.

"I am concerned that any tolerability data obtained in clinical trials won't necessarily be generalizable to broader populations of typically older, less fit patients who may be less amenable to greater side effects than the selected patients who choose to pursue clinical trials, and these patients are still going to be treated by physicians with far less support and experience than those who participated in the clinical trials," he told *Scrip*.

Herbst said that as co-leader for the Lung Master Protocol (Lung MAP) trial, which tests multiple drugs, he has been impressed that the combination can be managed well in the community setting, with education of oncologists.

The '067 study in melanoma "doesn't in any way affect my thoughts as we await lung cancer data," Herbst told *Scrip*.

Results from AstraZeneca PLC's MYSTIC study of its CTLA-4 inhibitor tremelimumab with its PD-L1 inhibitor durvalumab in first-line lung cancer are due mid-year and Bristol's CheckMate 227 study is expected early in 2018.

West also noted recent changes to plans for the CTLA-4/PD-1 combinations. Bristol announced Jan. 19 that it was not going to seek accelerated approval for the Yervoy/Opdivo combination after all, based on "a review of data available at this time." This followed news that AstraZeneca was changing the design of its MYSTIC study to include overall survival as a co-primary endpoint along with progression-free survival and give more weight to durvalumab as a monotherapy.

"We will need to see what the actual results in Phase III lung cancer trials demonstrated, but I don't think that we should presume that such a combination is likely to fundamentally change the treatment landscape … Even if the trial results are positive, I strongly suspect that the combination would be used selectively, likely quite sparingly, in community practice, given how many patients have a relatively compromised functional status," West said.

Meanwhile, Merck awaits a decision on a filing for accelerated approval of its PD-1 inhibitor Keytruda for use in combination with chemotherapy in first-line lung cancer.

AACR 2017: 'THE YEAR OF IDO'

Brad Loncar, CEO of Loncar Investments, commented that Yervoy has been falling out of favor – the toxicity of the combination "is the biggest bugaboo," though people have always known it was toxic. What really attracted attention was Bristol's release about the change in plans for the '227 study, which to investors implied that the company had seen some data that looked disappointing, Loncar told *Scrip*. AstraZeneca's decision to postpone the release of MYSTIC data from January to the middle of this year and change the trial design to have a larger monotherapy component was also concerning.

In addition to NewLink's positive Phase II data for the IDO inhibitor indoximod at AACR, both Bristol and Merck said they will be expanding collaborations to develop their PD-1 inhibitors with Incyte's epacadostat, in announcements coinciding with the meeting. Merck already had a Phase III study up and running of epacadostat in melanoma and will be running registrational studies in six additional tumor types, including two in NSCLC. Bristol will be launching two new registrational studies of Opdivo/epacadostat, one in first-line NSCLC and one in first-line head and neck cancer. This aggressive push by two leaders in immuno-oncology leads investors to believe the IDO/PD-1 combination has real legs.

At the minimum Bristol's new development plans with Incyte makes it look like they are "spreading their bets," and at the maximum it looks like PD-1/IDO is the more appealing option and the company doesn't have the luxury of time to wait around for its own IDO inhibitor to go through the whole development process, Loncar observed.

This AACR "was the year of IDO," with PD-L1/CTLA-4 falling a bit more out of favor and PD-L1/IDO emerging as the most hopeful replacement for it, Loncar suggested.

BMO Capital Markets analysts concluded that the IDO/PD-1 combination looks better tolerated than the combination of PD-1 with chemotherapy or Yervoy and that Merck gained an edge coming out of the meeting.

BMO analysts are expecting more promising data for the PD-1/IDO combination at the American Society of Clinical Oncology annual meeting in June, "which will probably provide the rationale for Merck and Bristol's decisions to advance it to pivotal trials," Arfaei said.

Mass General's Flaherty said that the data presented at AACR reinforce the promise of the IDO/PD-1 combination, especially in terms of safety, but also acknowledged the usual hazards of drawing conclusions based on small uncontrolled trials, in that the results could be due to statistical chance. The epacadostat/Keytruda combination was moved fast to Phase III in melanoma based on data from a single-arm study of 19 patients. NewLink had single-arm data for 60 patients at AACR. It would be easier to get more excited about the efficacy results from small, uncontrolled combination trials if they focused on patients with features that make them less responsive to PD-1 inhibitors, Flaherty said.

Yale's Herbst commented that a lot of novel classes are being studied right now in combination trials – such as IDO, LAG-33, TIM-3 and CD127 – but they are all still in early stages of development. PD-1/CTLA-4 is by far at the top and there is not enough data to suggest that any of the new combinations could compete, the clinician said. There's a lot of work ahead to figure out which to move forward to big Phase III studies, he said. "The entire community is trying to figure that out right now," Herbst said.

BMO analysts advised that the IO market is rapidly evolving and will become increasingly fragmented, as evidenced by the broad range of possible IO combinations for multiple tumors.

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What Could Come After CAR-T? Cue Is Betting On Selective Biologics

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Cue Biopharma, a young biotech formed on the basis of research from the Albert Einstein College of Medicine, is developing biologics engineered to selectively modulate disease-relevant T-cells to treat cancer – technology it has called the "next wave" in cancer immunotherapy.

Cue Biopharma Inc., a company developing biologics targeting tumor specific T-cell receptors (TCRs), believes its technology could represent the next wave of cancer immunotherapy – besting even novel chimeric antigen receptor (CAR) T-cell therapies that are yet to reach the market. Still, while Cue is excited about its technology based on promising preclinical data, lots of uncertainties remain around the mechanisms of action for biologic cell therapies.

Cue's hypothesis is based on using biologics to stimulate existing T-cells with endogenous T-cell receptors – unlike CAR-T therapy this does not involve modifying the cells. Its biologics generate tailored immune responses in disease-relevant T-cell populations by emulating signals, or cues, delivered by the body's antigen presenting cells (APCs).

"In developing Cue's technology way back when, we wanted to leverage the potency of co-stimulators but restrict the effect to only disease relevant T-cells. In doing this we hoped to remove the dose-limiting toxicity barriers that plague the globally acting cancer immunotherapies we have currently," VP and head of R&D Ronald Seidel told *Scrip*.

Cue's lead compound, Cue-101, which is being trialed for human papillomavirus (HPV)-associated cancers such as cervical and anal cancers, has just reached the IND stage and is expected to enter Phase I in the first half of 2018. With Cue-101, the company is targeting the HPV-E7 epitope in combination with IL-2 therapy. Cue expects the Phase I study to be in cancer patients and it aims to gather a wealth of information about the drug treatment including efficacy data. The company will then follow a registrational path from Phase II.

Cue Biopharma

Location: Cambridge, MA

R&D Focus: biological T-cell immunotherapy

Disease Area(s): cancer and autoimmune disorders

Founding Date: June 2015

Founders: Dr Ronald D. Seidel, Dr Rodolfo J. Chaparro and Dr Steven Almo

Employees: 16

Financing Total To Date: $26M

Investors: MDB Capital Group

Comparing its technique to CAR-T therapies, Cue's management said the biggest difference would be ease of scaling up production for their fusion biologics. Manufacturing of CAR-T therapies is expected to be a logistical hurdle for the first wave of developers. Current CAR-T candidates are individualized to patients, which makes widespread manufacturing challenging and labor intensive.

A 2016 article in the American Society of Gene & Cell Therapy's official journal, on the manufacturing of CAR-T therapies, notes that partnerships between industry and academic centers "accelerate development and promote future commercialization prospects" for CAR-T products. For example, Juno Therapeutics Inc. works with Memorial Sloan Kettering Cancer Center, Novartis AG with the University of Pennsylvania, and Kite Pharma Inc. with the National Cancer Institute.

Meanwhile, like Cue, Kite Pharma is also investigating TCR candidates directed against HPV-16 E6 and E7 oncoproteins for the treatment of HPV-associated cancers. In 2016, the company signed a deal with the US National Cancer Institute (NCI), under which the latter partner will research a new TCR therapy candidate targeting HPV-16 E7 as a both a monotherapy and in combination with a (as yet unnamed) checkpoint inhibitor in HPV-16 associated solid tumors. This Phase I/II study will be led by Christian Hinrichs from the experimental transplantation and immunology branch of the NCI.

Founded in June 2015, Cue's platform was developed at the Albert Einstein College of Medicine as part of a five-year, specialized center grant from the National Institutes of Health (NIH). This funding enabled the technology to be built into an industry-scale, drug design platform capable of rapid and efficient molecular prototyping and development.

The business was founded by Seidel; Rodolfo Chaparro, the current head of immunology; and Steven Almo, who is chair of the company's scientific advisory board and the chair of the department of biochemistry at Albert Einstein College of Medicine. All three were employees at the college developing Cue's technology, but Seidel and Chaparro left the academic establishment to progress Cue Biopharma as a business.

The company is headed by president and CEO Dan Passeri, who joined Cue from Curis Inc., a publicly traded firm developing small molecules for cancer, where he was president, CEO and vice chair of the board.

Despite being a young biotech focused on the crowded immuno-oncology development space but in the riskier area of cell therapy, Cue has managed to secure a substantial $26m from private capital funding, to date.

The company told *Scrip* it has already attracted great interest from potential pharma partners. "We haven't launched a formal business development effort but we have been getting pull. We have over 20 pharma companies engaged in discussions," Passeri said.

UNIQUE NOT NOVEL

"I've been in oncology my entire career and the field of immuno-oncology is the emerging frontier, but what is still needed in this field is the ability to target disease relevant parts of the immune system as opposed to the global shotgun approach we see today," Passeri told *Scrip*.

"Current IO therapies have opened the door for immune modulated approaches but there is still a tremendous need from a clinical efficacy standpoint and a tolerability standpoint to tailor treatments and better target disease relevant parts of the

immune system," Cue's CEO said, adding that the biotech's focus on targeting and modulating T-cells could achieve this goal.

Biomedtracker analyst Robert Jeng told *Scrip* that Cue's approach is interesting but he doesn't anticipate great leaps forwards in efficacy with compounds from the company. "The fusion molecule is certainly unique, but neither element is truly novel in the sense of evaluating a completely untested target," Jeng said. "Peptide-MHC complexes are well-studied and the IL-2 signaling element in the company's lead compound, Cue-101, is one of the oldest known immune activators. I would be surprised to see a major leap forward in efficacy over IL-2 alone," he said.

Cue is the only company currently looking at developing a fusion of a soluble peptide and a potent co-stimulator into one soluble biologic that can be manufactured at scale. This method creates "focus bursts of the immune system against tumor cell targets," Seidel said. The company's hope is that while demonstrating efficacy, its approach will bypass the serve toxicity effects associated with IL-2.

"T-cells are so dangerous, that's why they work to keep us safe against pathogens and tumors most of the time," Chaparro said, adding: "what is different about us, is that we think [we] can turn these on selectively."

There are other companies looking at activating T-cells but they are not doing it selectively, Chaparro said. "There are companies that have tried to do this selective activation recently with nanoparticles, like NexImmune Inc., but this has some drawbacks. It is hard to control the signals carefully as nanoparticles are quite large. It is also difficult to manufacture with any kind of robustness. Maybe someday this will work, but right now it is not working," he said.

Cue also has a second preclinical program, for candidate Cue-102, that is targeting the NY-ESO peptide. This program is focused on melanoma, synovial sarcoma and prostate cancers. NY-ESO is not a novel target for cancer immunotherapy and it is the same peptide at the center of Adaptimmune Therapeutics PLC's lead program. In partnership with GlaxoSmithKline PLC, Adaptimmune is currently conducting multiple Phase I/II clinical trials for its NY-ESO TCR therapeutic candidate in patients with solid tumors and hematological malignancies.

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Vifor Becomes A 'Pure Play' Pharma

A Swiss IPO for retail pharmacy and distributor spin-off Galenica Santé has allowed the remaining specialty firm Vifor Pharma to become a pure play pharma with a potential blockbuster potassium binder Veltassa and interests in renal disease, iron replacement and cardio-renal disorders.

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Key targets this year for Vifor Pharma Group, the new specialty company to emerge from the separation of Galenica's pharmaceuticals and health businesses into two companies, include the EU approval of the hyperkalemia therapy *Veltassa* (patiromer), with launch expected in the second half of 2017, and approval of the biosimilar, *Retacrit* (epoetin zeta, licensed from Pfizer Inc. for the US dialysis market), in late 2017 or early 2018.

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Nephrology is set to be one of three key areas for Vifor Pharma Group, formerly known as the Galenica Group, now that the company's health, beauty and well-being businesses have been placed in a separate company, Galenica Santé, with the help of an IPO on the Swiss Stock Exchange, SIX, that raised CHF1.9bn ($1.9bn).

The proceeds of the IPO, completion of which was announced on April 7, are being used to repay debt related to the acquisition of the US pharma company Relypsa Inc. for $1.53bn in the third quarter of 2016, and other projects. Following the IPO, Vifor is free of net debt.

Vifor Pharma Group remains listed on SIX, and is forecasting that its net sales should grow by high single-digits in 2017, while EBITDA should increase by a mid- to high-single digits, excluding launch costs for Veltassa of around CHF260m. Veltassa was approved for marketing in the US in 2015, and US sales are rising, with the product addressing a life-threatening unmet medical need, Vifor says.

The company is also likely benefiting from the delayed approval of AstraZeneca PLC's potential competing potassium binding product, *ZS-9* (sodium zirconium cyclosilicate) which received a second complete response letter from the FDA in March 2017 owing to manufacturing issues.

However, in Europe, the competitive landscape is more finely balanced, with ZS-9 cleared by the CHMP in February 2017, meaning it could be approved and launched later in 2017, as *Lokelma*.

Vifor is a leader in iron deficiency, nephrology and cardio-renal therapies, and is aiming to invest CHF850m in develop and launch new products over the next three years, including in the ongoing launch of Veltassa in the US, following its approval there in 2015. It is also aiming to expand the market for the injectable iron replacement product, *Ferinject* (ferric carboxymaltose) that was approved in the US in 2013 under the name Injectafer.

In development, Vifor has a ferroportin iron over-load inhibitor expected to enter Phase I in the fourth quarter of 2017, and has in-licensed several pipeline products, including ChemoCentryx Inc.'s complement C5a receptor inhibitor, avacopan (CCX168), for which Vifor has rights outside of the US and China, and has an option on CCX140, that could enter Phase III in 2017. Further in-licensing deals are expected during 2017.

Vifor Pharma Group consists of Vifor Pharma; Vifor Fresenius Medical Care Renal Pharma Ltd., owned 55% by Vifor Pharma Group and 45% by Fresenius Medical Care; Relypsa Inc; and OM Pharma.

In contrast, Galenica Santé operates more than 500 pharmacies in Switzerland, has its own range of OTC and branded products, and is a pre-wholesaler and wholesale distributor in the country. Its IPO, the largest for several years in Switzerland, came in at the top of the original price range, at CHF39.00 per share, and was several times over-subscribed; the company's market capitalization is CHF1,950 million.

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Cipla/Sandoz Gearing For Seretide Challenge In Australia?

Cipla Ltd. and Sandoz Pty Ltd appear to have received registrations for their respective fluticasone propionate/salmeterol therapies in Australia – the Indian firm for its metered dose inhaler, while Sandoz for its *AirFluSal Forspiro* 500/50 fluticasone propionate/salmeterol xinafoate actuation powder for inhalation. Cipla has received registration for fluticasone propionate and salmeterol in two strengths – 125/25 µg and 250/25 µg, particulars culled from the Australian Therapeutic Goods Administration website suggest. The Cipla product has been indicated for "regular treatment of asthma, where the use of a combination product is appropriate". This may include patients on effective maintenance doses of long-acting beta-2 agonists and inhaled corticosteroids and patients who are symptomatic on current inhaled corticosteroid therapy, details in the public Australian Register of Therapeutic Goods (ARTG) summary say. It also lists the symptomatic treatment of patients with severe COPD and a history of repeated exacerbations who have significant symptoms despite regular beta-2 agonist bronchodilator therapy.

anju.ghangurde@informa.com, 13 Apr 2017

US Tax Reform Simmers

US corporate tax reform is arguably the single policy change pharmaceutical manufacturers most want President Trump and the Republican-led Congress to get done, but now it appears a tax overhaul will be delayed until after Congress takes another swing at health care reform. "We're going to have a phenomenal tax reform, but I have to do health care first," Trump said in an interview on the Fox Business Network April 12. "If you look at the kinds of numbers that we're talking about, that's all going back into the taxes. And we have to do health care first to pick up additional money so that we get great tax reform," he said. Trump's comments appear to be a reversal, suggesting Congress will make another attempt to repeal the Affordable Care Act. Originally, Trump said he would pivot directly to tax reform after the Republican's initial repeal and replace plan, the American Health Care Act, was withdrawn from the House March 24 before a vote because the bill failed to gain enough Republican support.

jessica.merrill@informa.com, 12 April 2017

Biocad's Asian Biosimilars Play Undaunted By Roche

Russian biotechnology company Biocad appears to be on course to substantially expand the supplies of its biosimilar rituximab in Vietnam, a market that it has been engaged with since 2015. Biocad's rituximab is a biosimilar of *MabThera/Rituxan* and innovator Roche is a dominant player in Vietnam. The Russian firm said that last month it had been permitted to supply rituximab to Vietnam for a second time – implying continued access to its product at Vietnamese hospitals via the Russian company's local partners. But Biocad now expects to receive a permanent registration certificate for the medicine at the end of the third quarter or beginning of the fourth quarter of 2017, a move that is expected to facilitate export of the product to Vietnam from Russia "without any limitations". Biocad told *Scrip* that while a permanent registration (as well as quotas) gave the company "no preference" for supplies in Vietnam, the current quota for rituximab means that the company can import only limited amounts into the country. "After obtaining a permanent registration, we will be able to bring in the drug in accordance with the hospitals' need for rituximab. If there is a demand from Vietnamese hospitals, we can assert our supply capacity and provide as much drug product as needed," Biocad explained.

anju.ghangurde@informa.com, 10 April 2017

Galena/ImmunoCellular Caught In US SEC Clampdown

The former CEOs of Galena Biopharma Inc. and ImmunoCellular Therapeutics Ltd. received the harshest penalties in Securities and Exchange Commission enforcement actions against four biopharma companies for fraudulently promoting their stocks. They agreed to settlements that bar them from serving as an officer or director of any entity that has registered securities for five years. In addition, Galena's former CEO Mark Ahn must pay a disgorgement of $677,250 plus prejudgment interest of $67,181 and a civil penalty of $600,000 for a total of $1.3m. And ImmunoCellular's former CEO Manish Singh must pay disgorgement of $1.75m plus prejudgment interest of $151,676 and a civil penalty of $1m for a total of $2.9m. Singh also is the former CEO of Lion Biotechnologies Inc. The SEC issued cease-and-desist orders against four drug companies – Galena, ImmunoCellular, Lion and CytRx Corp. – alleging they hired communications firms that paid writers to publish positive articles about their stock without disclosing their compensation. The companies and two former CEOs submitted offers of settlement, which the SEC accepted, and consented to the cease-and-desist orders without admitting or denying the commission's findings. The drug companies and former CEOs were among 27 individuals and entities the SEC charged with the stock promotion scheme. The commission also filed fraud charges against seven stock promotion or communications firms, six individuals at the firms and nine writers. Of those charged, 17 have agreed to settlements that include disgorgement or penalties ranging from approximately $2,200 to nearly $3m.

brenda.sandburg@informa.com, 11 Apr 2017

Grünenthal Acquires Adhesys Medical

Grunenthal GMBH, the privately owned mid-sized German pharmaceutical company, is expanding its medical device R&D pipeline by acquiring Adhesys Medical GMBH, and its US-based affiliate Adhesys Medical Inc., focused on the development of adhesives used in surgery. Financial details of the deal have been kept confidential. The acquisition of the highly innovative pipeline of surgical sealants, together with the underlying technology platform, should allow Grünenthal to tap into the global $1bn surgical sealants market. Last year, the two companies signed an exclusive license agreement for the commercialization of innovative surgical glue in the EU and Latin America to provide patients with a topical wound closure alternative. The innovative technology platform Grünenthal has acquired should allow the development of topical adhesives for usage on the skin, the first of which is expected to receive European-wide CE Marketing Certification within the next 12 months with the development of surgical sealants for wet wounds, which is already ongoing. The company says the products will enable next generation wound closure such as in cardiac and gastrointestinal surgery – an area of surgery with a high unmet need with regard to innovative wound closing techniques. While the medical device area is a relatively new area of focus for Grünenthal, the acquisition is in line with company's five-year business plan.

mike.ward@informa.com, 10 April 2017

Biogen Builds In Neurodegenerative Disease

Biogen Inc. plans to move quickly to study its new tau antibody in Phase II clinical trials in Alzheimer's disease and progressive supranuclear palsey (PSP) after licensing it from Bristol-Myers Squibb Co. The company announced a licensing agreement with Bristol to acquire worldwide development and commercialization rights to the investigational drug April 13. Biogen agreed to pay $300m upfront, as well as $410m in additional milestones and royalties. Bristol, under pressure after losing competitive ground in its core focus area of immuno-oncology, is presumably not looking to invest in the late-stage development of the drug, which it gained with the acquisition of iPierian Inc. for $175m upfront in 2014. Biogen will be responsible for paying the outstanding milestones due to iPierian shareholders under the deal with Bristol – $550m in remaining milestones plus royalties. For Biogen, the deal suggests the biotech is doubling down in the high-risk area of neurology, specifically in Alzheimer's disease and other neurodegenerative diseases. Biogen has been heavily investing in and developing notable expertise in this field of research. In an interview at the J.P. Morgan Healthcare Conference in January, Exec VP-R&D Michael Ehlers talked about how neuroscience has hit an inflection point and why he is so enthusiastic about the opportunities for drug development in the field. Getting investors energized about developing drugs for some of the most challenging neurodegenerative diseases hasn't been easy for Biogen, however, especially as growth of its blockbuster multiple sclerosis pill *Tecfidera* (dimethyl fumarate) has plateaued. Investors have been especially keen to see Biogen bring in a late-stage pipeline candidate or commercial-stage asset, given that the company's pipeline is largely in early- to mid-stage development. Biogen's new CEO Michele Vounatsos only took over the helm at the start of the year, but so far it appears the company is sticking to a deal playbook that is similar to the one under former CEO George Scangos – early-stage, neuroscience opportunities.

jessica.merrill@informa.com, 13 April 2017

Fresenius Steps Up International Ambition

Following on from its acquisition of Spanish private hospital group Quironsalud for $6.1bn in 2016, Fresenius SE & Co. KGAA is in talks to acquire US company Akorn Inc.; the generics firm is currently valued at around $3.7bn, which includes an 18% premium following a share price surge when news of the discussions broke. Akorn generated around $1.1bn in sales in 2016. Fresenius promoted its CFO Stephan Sturm to the CEO role in July last year. According to Jefferies analyst Chris Cooper, Akorn has long been viewed "as an attractive takeover target given its $1bn top-line, high-margin, niche generics business, full US tax rate, low leverage and deep maturing pipeline of 90 ANDAs on file at FDA representing $9.5bn in value." In an April 10 research note, Cooper added that 36 of these ANDAs – equivalent to $4.2bn in revenue value – have already been under review for more than 36 months. "Despite headwinds in 2017 from greater ephedrine competition, Akorn is poised for strong top-line growth in the coming years, driven by new launches," he said. Morningstar analyst Michael Waterhouse, in an April 10 research note, concurred. He also considers Akorn to be a popular takeover target thanks to the firm's "focus on more complex generic drug products, which creates higher barriers to entry and therefore more price stability than seen in more conventional segments of the generic market." He suggested Fresenius' generic injectable drug manufacturing operations would likely create manufacturing cost synergies and improved scale through combining the two firms. "Additionally, Akorn enhances Fresenius' US market product portfolio and exposure, similar to the firm's acquisition of injectable drug manufacturer APP in 2008," he noted.

sukaina.virji@informa.com, 11 April 2017

Insulin Resistance Is Underlying Key To NASH

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The former Octeta is expanding the ongoing Phase IIb study of its second-generation insulin sensitizer. An insulin sensitizer with a better safety profile than first-generation drugs like Actos may provide a backbone therapy for NASH, the company believes.

With $40m in Series A cash and led by a new, experienced executive team, Cirius Therapeutics Inc. is expanding a Phase IIb dose-finding trial of its insulin sensitizer MSDC-0602K in non-alcoholic steatohepatitis (NASH) in the hopes that a safer, second-generation drug can address the disease's underlying metabolic pathology.

Formerly known as Octeta Therapeutics, the company builds upon the research of Jerry Colca, one of the project leaders behind the development of the first-generation insulin sensitizer pioglitazone (Takeda Pharmaceutical Co. Ltd.'s *Actos*) at Upjohn. A co-founder and VP of research and development at Cirius, Colca has performed preclinical studies showing that MSDC-0602K offers significant potential in resolving NASH and reducing fibrosis in NASH patients, Cirius CEO Bob Baltera told *Scrip*.

Baltera, along with fellow former Laguna Pharmaceuticals Inc. execs Howard Dittrich and Brian Farmer, signed on with Frazier Healthcare Partners, which is backing San Diego-based Cirius, as entrepreneurs in residence. Colca remains at Octeta's original Kalamazoo, Mich., location, and lined up the $40m Series A, in which Novo A/S, Adams Street Partners, Renaissance Capital Venture Fund and existing Octeta backer Hopen Life Sciences Ventures also participated. The round adds onto $16m previously raised by Octeta, and will enable the ongoing EMMINENCE study to be expanded from roughly 200 patients to between 300 and 350, Baltera noted.

A selective modulator of metabolism via the mTOT (mitochondrial target of thiazolidinediones) pathway, MSDC-0602K is thought to offer a better safety profile than pioglitazone and other first-generation compounds because it doesn't work predominantly through PPAR (peroxisome-proliferator-activator-receptor) gamma, which has been associated with weight gain, edema and bone loss. Actos and other pioglitazone-containing drugs carry warnings for risk of heart failure and for bladder cancer.

MSDC-0602K, originally discovered by Metabolic Solutions Development Co. LLC, which spun out Octeta in January 2016 to focus on the drug in NASH and polycystic kidney disease, is one of four NASH candidates in clinical development that target the PPAR pathway.

The others are Genfit SA's Phase III elafibranor, a dual agonist of PPAR alpha and delta; Inventiva Pharma's Phase IIb INV-337, a triple agonist of PPAR alpha, gamma and delta; and Zydus Cadila's *Lipaglyn* (saroglitazar), a dual agonist of PPAR alpha and gamma. Lipaglyn was approved in India in 2013 to treat diabetes dyslipidemia before the company decided to investigate its potential in NASH.

PLENTY OF ROOM

Even though the NASH drug development race is packed with dozens of candidates and competing companies, Baltera said the draw of a different approach in NASH drew him because it's probably the hottest therapeutic space after immuno-oncology.

"That's because 80m Americans have non-alcoholic fatty liver disease, 16m have NASH, [and] probably it's going to be a disease in which a multi-drug approach will [prevail] in the future," he said. "You see a lot of anti-fibrotics being developed in the space, there are a lot of anti-inflammatory compounds, but what you don't necessarily see so much is a lot of effort around insulin-sensitizer compounds. One observation would be that 60%-80% of NASH patients are type 2 diabetics, so it appears that insulin resistance is a root cause that sort of starts the process."

Proof-of-concept for MSDC-0602K is provided by Phase II data of the drug in type 2 diabetes patients. As far as mid-stage NASH testing, there has only been a very small investigator-driven Phase IIa that Baltera said had "fewer than five patients." The revised EMMINENCE trial includes four arms, testing three different doses of the study drug against placebo with patients treated for one year and assessed before dosing and at the end of the year with a liver biopsy. Cirius' main concern for the Phase IIb trial is to determine the minimum effective dose, because safety is a bigger worry than efficacy at this point, Baltera said. The study uses a primary endpoint of hepatic histological improvement, measured by improvement in non-alcoholic fatty liver disease score (NAS) by at least two points with no concurrent worsening of fibrosis over 12 months.

Cirius expects to have data from the study by 2019, at which time it will determine a strategy for moving forward.

"Assuming we get efficacy in some way, shape or form with the three doses – let's assume that as you move up in doses, you get more and more potency and efficacy – at some point, the real decision you need to make as a drug developer is what's the therapeutic window," Baltera explained. "If I get a lot of efficacy but I have a lot of overhang of safety or tolerability, it's not very informative. … We think if we have that, we'll put together a strategy that will lend itself to either a good financing or a good partnership, whatever makes the most sense for us."

MONOTHERAPY AND COMBOS

Despite the heavy competition in the NASH space, Baltera said getting investors for the Series A was not too difficult – he got no sense that investors think the opportunity in NASH already has passed. Even if the first drug therapy for NASH has been approved by the time Cirius obtains its Phase IIb data in 2019, he thinks there will be plenty of space in the treatment paradigm for new entrants.

"If we're successful as an industry, there's going to be room for lots of therapeutic intervention there," the exec said. "And I think what you've seen from some of the results to date is that nothing has lent itself to being the magic bullet."

Published online 11 April 2017

Hilleman's Shigella Vaccine Set For Trials

Hilleman Laboratories' quest to get the first ever approval for a Shigella vaccine marks a significant shift in strategy for the Indian company, which up to now has specialized in optimizing existing vaccines by making them cheaper, more effective and simpler to use, rather than focusing on developing novel products for unmet health needs. The New Delhi-based firm - an equal partnership between Merck & Co. Inc. and the UK's Wellcome Trust - has teamed up with India's state-run National Institute of Cholera and Enteric Diseases (NICED) to further develop and commercialize the pioneering vaccine for shigellosis, a form of bacillary dysentery that is one of the leading causes of death among children under five in developing countries, but has so far proved an elusive vaccine target. Intensive research efforts have been underway for more than six decades to develop an effective vaccine, but researchers have been frustrated by these multiple different strains, which produce toxins that attack the lining of the large intestine, causing potentially fatal swelling, intestinal wall ulcers, and bloody diarrhea.
Penelope MacRae, 11 April 2017

Imetelstat Trial Update Lift Geron

Geron Corp.'s clinical update news that studies of the telomerase inhibitor imetelstat will carry on in lower risk myelodysplastic syndromes and relapsed/refractory myelofibrosis gave the company a boost in the market, even though partner Johnson & Johnson has not committed to more advanced development. The Phase II/III IMerge study of lower risk myelodysplastic syndromes (MDS) will continue with some revisions, subject to approval by the US FDA, and the Phase II IMbark of relapsed/refractory myelofibrosis (MF) will carry on with no changes, based on a new internal data review, Geron announced April 10. The company's stock price rose by 19.53% on the news, closing at $2.57, even though global partner Janssen Pharmaceutical Cos., a J&J company, has not committed to development over the longer term. Geron has been partnered on imetelstat (GRN163L) with Janssen since November 2014; the deal included an upfront payment of $35m and up to $900m in milestone payments and gave Janssen worldwide development and commercialization rights in oncology, including hematologic malignancies. Per the agreement, Janssen needs to make a decision about moving forward with development after a Phase II analysis or after the start of Phase III within a certain time period.
emily.hayes@informa.com, 10 April 2017

Stada To Act As 'Core' For Future Bain and Cinven Bolt-Ons

Private equity firms Bain Capital and Cinven Partners LLP are buying German generics maker Stada Arzneimittel AG at an eye-watering takeover price to use its products and infrastructure as a core business around which smaller bolt-on deals can coalesce into a sizeable entity for an eventual sale, analysts say. Stada April 10 agreed to sell itself to Bain and Cinven for €5.3bn ($5.6bn) – giving the duo control of one of the last independent generic drug manufacturers in Europe – after they won a dramatic takeover competition with a sweetened joint offer. Together they are paying €65.28 plus a dividend of €0.72 per Stada share, the Bad Vilbel-based drug maker said in a statement. That's 49% above where Stada's share price traded on Dec. 9 when talk of a takeover first surfaced. The decision to sell is a victory to Stada's activist shareholders and caps years of struggle during which the firm's entrenched management avoided a takeover through use of an unusual shareholder structure. But an uprising in 2016 by investor Active Ownership Capital (AOC) opened the way to the current transaction. Explaining its choice of buyer, achieved via a structured bidding process, Stada's management said "a contractual agreement was reached to the effect that Bain Capital and Cinven would strengthen Stada's position as a globally active pharmaceutical company, support its growth strategy and thus contribute to a long-term increase in the company's value...Bain Capital and Cinven have agreed to provide both financial and strategic support for possible acquisitions to expand the product portfolio and tap new growth markets."
sten.stovall@informa.com, 10 April 2017

Mogamulizumab Nips At Adcetris's Heels In CTCL

Kyowa Hakko Kirin Co. Ltd. says it plans to initiate discussions with regulatory authorities this year about pursuing marketing authorizations for mogamulizumab in cutaneous T-cell lymphoma (CTCL), following just-released positive top-line results from a comparative Phase III trial. The new findings position the CCR4-targeting antibody as a likely "close follower" in the CTCL setting to *Adcetris* (brentuximab vedotin), an antibody-drug conjugate being developed by Seattle Genetics Inc. and Takeda Pharmaceutical Co. Ltd. (which has ex-US rights) that is also scheduled for a US approval submission sometime later this year. In what the Japanese firm says is the largest such international randomized study in the indication, the met its primary endpoint of a statistically significantly improvement in progression-free survival compared with vorinostat, a histone deacetylase inhibitor already marketed for CTCL by Merck & Co. Inc. as Zolinza. The MAVORIC study was conducted in 372 CTCL patients who had failed at least one prior systemic treatment.
ian.haydock@informa.com, 12 April 2017

Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage, Phase III clinical trial developments for the more than 10,000 drug candidates under active research worldwide. To see changes to the progress of product candidates further back in the development pipeline, and a table of the week's product approvals, please visit our Pipeline Watch webpage at scrip.pharmamedtechbi.com.

CLICK

Visit the Pipeline Watch webpage at scrip.pharmamedtechbi.com for all the week's changes to the industry's R&D pipeline

Selected clinical trial developments for the week 7–12 April 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Updated Phase III Results			
Aerie Pharmaceuticals Inc.	*Rhopressa* (netarsudil)	glaucoma	Rocket 4 study; positive safety and efficacy results.
Phase III Interim/Top-line Results			
Sumitomo Dainippon Pharma Co. Ltd.	dasotraline (SEP-225289)	attention deficit hyperactivity disorder	Study 305; met primary endpoint in children.
Kyowa Hakko Kirin Co. Ltd.	mogamulizumab	cutaneous T-cell lymphoma	MAVORIC; met primary endpoint, longer PFS versus vorinostat .
Phase III Initiated			
Nabriva Therapeutics AG	lefamulin	community acquired bacterial pneumonia	LEAP-1; patient recruitment completed.
Phase II Suspended			
OncoMed Pharmaceuticals Inc. /Celgene Corp.	demcizumab (anti-stem cell therapeutic)	pancreatic cancer	YOSEMITE; missed primary endpoint, study discontinued .
Updated Phase II Results			
Protalix BioTherapeutics Inc.	alidornase alfa (AIR DNase)	cystic fibrosis	Expressed in plant cells, a modified DNase enzyme.
AbbVie Inc./Neurocrine Biosciences Inc.	elagolix	heavy menstrual bleeding in patients with uterine fibroids	Effective and rapid reduction in symptoms.
Medivir AB/TetraLogic Pharmaceuticals Corp.	remetinostat gel	cutaneous T-cell lymphoma	Complete or partial responses seen.
Phase II Interim/Top-line Results			
Highland Therapeutics Inc.	HLD100 (amphetamine) delayed and extended release	attention deficit hyperactivity disorder	Well tolerated in pediatric patients.
Novan Inc.	SB208 (a nitric oxide product) gel	tinea pedis	Shows a fungicidal effect.
Anthera Pharmaceuticals Inc.	blisibimod	IgA nephropathy	BRIGHT-SC; slowing of proteinuria progression.
Phase II Initiation			
argenx NV	ARGX-110, a CD70 targeting MAb	cutaneous T-cell lymphoma	In relapsed or refractory patients.
Transgene SA	*Pexa-Vec* (pexastimogene devacirepvec) oncolytic virus plus metronomic cyclophosphamide	sarcoma, HER2-negative breast cancer	METROmaJX; low-dose high-frequency cyclophosphamide.
Apexigen Inc./Bristol-Myers Squibb Co.	APX005M plus nivolumab	advanced solid tumors	An activator of the co-stimulatory receptor, CD40, and a checkpoint inhibitor.
Immunovaccine Inc. /Merck & Co. Inc.	DPX-Survivac plus pembrolizumab and low-dose cyclophosphamide	recurrent platinum-resistant ovarian cancer	A triple combo being evaluated in Canada.
Inotek Pharmaceuticals Corp.	trabodenoson and latanoprost	glaucoma	Will evaluate effect on the trabecular meshwork.
Idera Pharmaceuticals Inc.	IMO-2125 plus ipilimumab	metastatic melanoma	intratumoral admin. of TLR9 agonist, IMO-2125.
Five Prime Therapeutics Inc.	cabiralizumab	pigmented villonodular synovitis	Study 002; in 30 patients.

Source: Biomedtracker

Vladimir Paul-Blanc had been appointed president and general manager of **ThermiGen LLC**, an Almirall SA business. Paul-Blanc brings more than 13 years' experience in general management positions to the company and most recently he was general manager for Solta Medical. He will be replacing ***Paul Herchman*** (CEO) and ***Kevin O'Brien*** (president), who will move on to new non-executive roles as global strategic advisors to the Thermi Board.

ReForm Biologics has appointed ***John M. Sorvillo*** CEO. With over 25 years of experience in developing and licensing technologies, Sorvillo joins ReForm from Amgen where he was director of business development and licensing. Before this he was vice president of business development at Genocea Biosciences, VP of development at Altus Pharmaceuticals, VP of business development at ArQule and held various positions at OSI Pharmaceuticals including VP and general manager of the research products division.

Reinhard Kandera has joined **Hookipa Biotech AG** as chief financial officer (CFO) and has also been appointed to the company's management board – effective June 1, 2017. Kandera has 20 years of experience in finance and healthcare industries, including 15 years in senior executive roles within biotech companies. Before joining Hookipa, Kandera was member of the management board and CFO of Valneva SE. Prior to this he was CFO of Intercell AG.

Faron Pharmaceuticals Ltd. has appointed ***Gregory B. Brown*** and ***John Poulos*** to its board as non-executive directors. Brown brings 35 years of experience in healthcare and investment to the company. Most recently he founded a healthcare focused private asset management firm, HealthCare Royalty Partners, where he is vice chair. Brown is also director of Caladrius Biosciences Inc. and Nuron Biotech Inc., and previously he was a director of Invuity Inc. Meanwhile, Poulos has spent 38 years working for AbbVie and Abbott and most recently he was vice president, head of licensing and acquisitions for AbbVie and group vice president, head of pharmaceuticals licensing and acquisitions for Abbott Pharmaceuticals.

Iain Ross has been named chair of **Redx Pharma**'s board of directors and a non-executive director of the company – effective May 1, 2017. Ross has 35 years of experience in the life sciences industry and has held senior board and management positions at various public and private companies in the sector. Previously, he was executive chair at Silence Therapeutics plc, CEO of Allergy Therapeutics and Quadrant Healthcare plc, and main director of Celltech Group plc.

Ashfield, part of the healthcare services provider UDG Healthcare plc, has appointed ***Tom Mitchell*** head of syndicated services for the Ashfield Commercial business in the UK. Mitchell joined Ashfield Commercial business in 2008 as regional business manager and was later appointed project manager.

In addition to this news, **UDG Healthcare plc** has appointed ***Jez Moulding*** chief operating officer of the company and executive vice president of Ashfield – effective May 2, 2017. Moulding has spent 18 years at Sanofi where he held various senior leadership positions across the globe; most recently he was senior vice president and North America region head for diabetes and cardiovascular.

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